Remarks

Rejections under § 112

The Examiner stated:

The phrase "a recombinant antibody" claimed in claim 25, line 1, the phrase "a recombinant anti-LFA-1 antibody" claimed in claim 30, line 1, and the phrase "human antibody" claimed in claim 76, line 2, represent a departure from the specification and the claims as originally filed.

Applicant's amendment tiled 2/21/03 points to the specification for support for the newly added limitations "a recombinant antibody", "a recombinant anti-LFA-1 antibody" and "human antibody" as claimed in claims 25, 30 and 76 respectively. However, the specification does not provide a clear support of "a recombinant antibody", "a recombinant anti-LFA-1 antibody" and "human antibody". The instant claims now recite limitations which were not clearly disclosed in the specification and claims as originally filed.

Regarding claim 25, the term "recombinant anti-integrin antibody" is used, e.g., at page 26, line 3.

Regarding claim 30, the term "anti-LFA-1 antibody" is used, e.g., at page 12, line 29. LFA-1 is an integrin (see, e.g., at page 13, line 13). Accordingly, usage of the term "recombinant anti-integrin antibody", e.g., at page 26, line 3, clearly encompasses "recombinant anti-LFA-1 antibodies."

Claim 76 has been amended. Support can be found, e.g., at page 26, line 4.

Rejections under § 103

The Examiner stated:

10. Claims 25-27,29-31, 73-78, 80 and 82 are rejected under 35 U. S. C. 103(a) as being unpatentable over Huang et al (Proc. Natl. Acad. Sci. 94: 3 162-3 167, 1997), as is evidenced by Lu et al (Proc. Natl. Acad. Sci. 98: 2393-2398, 2002)in view of U.S. Patent No. 5,843,712.

The teachings of Huang et al and Lu et al cited as an evidentiary reference have been discussed, supra. Further, although Huang et al do not teach the specific antibodies bind to a modified integrin I-domain in the open conformation, the antibodies bind to an activation specific epitope (I domain)on the integrin, the antibodies blocks an interaction between an integrins and a cognate ligand, wherein said modified I-domain of an αL subunit contains amino acid substitutions K287CK294C or E284CYE301C and wherein modified LFA-1 I-domain contains amino acid substitutions K287CK294C or E284C/E301C, all these limitations are considered an inherent property of the reference antibodies.

As is evidenced by Li et al, that antibodies against αL I domain of LFA-1, BL5, F8.8, May. 035, TS1/22 and TS2/6 bind to the open or "active" mutants K287CK294C of aL subunit of LFA-1 "modified I domain" (see Table 1 page 2394 in particular). Furthermore, Lu et al teach that BL5, F8.8, May. 035, TS1/22 and TS2/6 antibodies

strongly inhibited binding of both wild-type and mutant K287CYK294C of aL subunit of LFA-1 (page 2395, Table 2 in particular).

The claimed invention differs from the reference teachings only by the recitation of a recombinant antibody, a human antibody in claim 76, a humanized antibody in claim 77, and a chimeric antibody in claim 78.

The Examiner is correct to state that the prior art antibodies bind to open or active mutants of αL with at least some affinity. However, the claims, as amended, require something significantly different than merely binding to an integrin in the open conformation. Claims 25-30, 73-80, and 82 require that the binding be specific for the open conformation relative to the closed conformation. Claims 83-87 require that the closed conformation not be bound within the limitations of background binding and other issues.

Careful examination of the table provided below, which summarizes the data from Table 1 of Lu et al. shows no antibody having the claimed properties.

	K287C/K294C [open conformation]		L289C/K294C [closed conformation]	
mAb	293T	K562	293T	K562
BL5	92 ± 11	92	86 ± 16	98
F8.8	94	102	84	94
TS2/6	85 ± 6	89	79 ± 3	96
May.035	93 ± 8	93	82 ± 14	101
TS1/22	96 ± 12	93	91 ± 8	110

The binding to the open or closed conformational mutants is almost equivalent among the antibodies or differs by only a few percentage points (the figures in the Table are given as a percentage of wild-type binding). Note, for example, for the only antibody for which binding to open is even nominally greater, the binding to the closed conformation – F8.8 – is still 84% of wild-type, hardly what one would call specific.

Note also that the relatively small differences between binding to the open and closed forms are highly cell-type dependent. The data recited in these tables were obtained from both 293T cells and K562 cells. The cell-to-cell differences for binding to the closed conformation and the cell-to-cell differences for binding to the open conformation are of similar magnitude as the differences between binding the open and closed conformation for the same cell-type. Again looking at F8.8, the difference in binding between the open conformation on 293T cells (94%)

and on K562 cells (102%) is about the same as the closed-open difference (94% v. 84% or 102% v. 94%).

Furthermore, the standard deviation, where available, has a magnitude about the same as seen between binding to open and closed for F8.8. Again, this is a far cry from the specific binding required by claims 25-30, 73-80, and 82 or the binding properties of claims 83-87 in which the antibodies do not bind to the closed conformation.

Thus, the prior art antibodies do not make obvious the claimed antibodies or antibody fragments.

With respect to the Examiner's remarks on page 3 of the action dated April 10, 2003, the Applicants note that the portions of the specification cited by the Examiner do not refer to antibody binding affinities. The Examiner remarked:

> **Further, as is evidenced by the specification on page 76, lines 7-8 and page 77, Table 6 that the affinity of E284C/E301C mutant is nearly comparable to K287CK294C mutant affinity (e. g.. predicted open conformation binds with high affinity).**

Page 76, lines 7-8 and Table 6 discuss the "kinetics of interaction of αL I-domains with ICAM-1." This portion of the specification does not discuss the affinity of antibodies for αL I-domains.

The applicants do not concede any positions of the examiner that are not expressly addressed above, nor do the applicants concede that there are not other good reasons for patentability of the presented claims or other claims.

This reply is being filed with a Request for Continued Examination and an Information Disclosure Statement. Enclosed is a $55 check for the Petition for Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 15775-029001.

Respectfully submitted,

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